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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,248	04/09/2001	Billy F McCutchen	BB1208PCT	4178

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,248	MCCUTCHEN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0901* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed February 24, 2003. Currently, claims 21-31 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group 1 in Paper No. 0203 is acknowledged.

Priority

3. This application claims priority as a 371 of PCT/US99/24922, filed October 22, 1999 and provisional application 60/105,404, filed October 23, 1998.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Drawings

4. The drawings are approved.

Claim Objections

5. Claim 26 is objected to as depending upon a cancelled Claim, namely Claim 1. Claim 21 is directed to a polynucleotide. Therefore, it appears as though Claim 26 contains a typographical error and should read Claim 21.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 21-31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claims are broadly drawn to an isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide having toxin activity wherein the polypeptide has an amino acid sequence of at least 95% sequence identity with SEQ ID NO: 9.

The specification teaches Zilbergberg determined that single amino acid residues are important for receptor binding and for biological activity of scorpion Na channel toxins (page 1, lines 19-20). The specification provides specific examples which

illustrate single amino acid changes cause a substantial decrease in biological activity and others change in structures. The specification also teaches that the role of Na-channels have been less clearly studied (page 1, lines 28-29). The specification briefly describes two toxins which have different chemical and pharmacological properties. The specification concludes that "thus, other toxins derived from scorpion venom will also have different chemical and pharmacological properties" (page 3, lines 5-10). The specification asserts that SEQ ID NO: 9 is a scorpion neurotoxin I polypeptide (page 3, lines 15-16). The specification compares the neurotoxin I of the instant invention (SEQ ID NO: 9) with the sequence of neurotoxin I from Buthus occitanus tunetanus (SE QID NO: 10) to illustrate the conserved cysteine residues (Figure 2). The specification vaguely alludes to toxin activity assays being confirmed using bioassay, LCMS or antibodies (page 16, lines 5-12). The specification asserts that the presence of toxin activity in the recombinant viruses will be monitored in vivo; compared to wild type; and analyzed using larvae to monitor behavioral changes and mortality (page 16, lines 5-12).

The sequence search illustrates that SEQ ID NO: 9 is 79.3% identical with an alpha insect toxin precursor from Leiurus quinquestriatus. Similarly, SEQ ID NO: 9 is also 75.7% identical with an anti-mammals neurotoxin Bmk9 precursor. The sequence search does not make it clear whether SEQ ID NO: 9 is either an insect or mammalian toxin.

The art teaches that scorpion venoms contain a variety of polypeptide toxins that specifically block or alter gating properties on ion channels (Moskowitz et al. Eur. J.

Biochem. Vol. 254, pages 44-49, 1998). Within these toxins exist small and large polypeptides; mammalian toxins and insect-selective toxins; inset-selective toxins can either be depressant toxins or excitatory toxins (page 44). Moskowitz provides a comparison between similarity between various classes of toxins (page 47). Sautiere et al. (Toxicon, Vol. 36, No. 8, pages 1141-1154, 1998) also provides various classifications between the different toxins.

The post filing date establishes the existence of at least three pharmacological groups of "long-chain" Na channel toxins characterized from the Chinese scorpion Buthus martensii Karsch (BmK) (Zhu et al. Toxicon, Vol. 38, pages 1653-1661, 2000). There three groups each have different pharmacological characteristics. The first group includes alpha-toxins which affect mammals and/or insects through slowing the sodium channel inactivation, such as BmK1, BmK2, BmK3 etc (page 1654). The third group includes depressants insect selective toxins, which induce progressive flaccid paralysis of insects, such as BmKIT2, BmKIT3 and BmKIT4. The fourth group contains the excitatory insect-selective toxins which cause rapid contractive paralysis of insects upon injection such as BmKIT1 (page 1654). It is clear that each of these "toxins" have different properties, different effects and affect different organisms. Zhu discusses placing 9 novel homologues into various groups based upon various differences in single amino acid residues (page 1659).

Neither the art nor the specification teach a specific and substantial utility for the claimed invention. First, the specification nor the art teaches a specific utility to the claimed nucleic acid. The general utility of the nucleic acid as a toxin is not specific

since the art teaches that scorpion toxins are classified into several categories based upon their size, toxicity to certain animals or insects and have different biological and pharmacological characteristics such as whether the toxins are depressant in nature or excitatory. The specification does not teach whether SEQ ID NO: 9 has any particular toxin activity. The specification has assigned SEQ ID NO: 9 as a toxin based upon homology to known toxins. While it is likely that SEQ ID NO: 9 is a toxin it is unpredictable whether SEQ ID NO: 9 is a toxin to mammals and/or insects and whether the toxin acts in an excitatory or depressant manner. The specification has provided no guidance as to the particular function, specificity or biological activities of SEQ ID NO: 9. Therefore, there is no specific utility for the claimed nucleic acid. Moreover, the nucleic acid lacks a substantial utility because the asserted utility as a toxin requires carrying out further research to identify or reasonably confirm a "real world" context of use.

Moreover, the specification fails to provide a clear definition of "having toxin activity." The dictionary provides that toxin is defined as poison produced by living organism (see askoxford.com). Moreover, poison has been defined as substance that when absorbed by living organism kills or injures it. Therefore, it is unclear how one may determine the level of toxin activity required for the claims and how the skilled artisan may determine whether a particular sequence has toxin activity.

With respect to the percent homology language used in the claims, the specification does not teach which particular amino acid residues are important for receptor binding and biological activity. The claimed variant nucleic acids lack specific and substantial utility since the specification has failed to provide any particular

characteristics with respect to SEQ ID NO: 9, it would be unpredictable how the skilled artisan could modify the sequence to maintain the particular function of SEQ ID NO: 9. It would require carrying out further research to identify or reasonably confirm a "real world" context of use, as described above, to determine the function, biological activity and the pharmacological nature of SEQ ID NO: 9. Furthermore, once the skilled artisan had determined how SEQ ID NO: 9 functions, to modify SEQ ID NO: 9 to maintain the function and properties of the wild-type sequence is unpredictable. The specification has not provided any particular regions or domains which are essential to the functioning of SEQ ID NO: 9 as a toxin. It is clear from the art, namely Zilberberg, that altering single amino acids within a toxin varies the properties of toxicity vastly (Table 1, page 14812). Therefore, while the skilled artisan could alter four of the amino acids within SEQI DNO: 9 (i.e. 95% identity), it requires further research to identify a "real world" context of use as to which changes may be made such that toxin activity is maintained.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to an isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide having toxin activity wherein the polypeptide has an amino acid sequence of at least 95% sequence identity with SEQ ID NO: 9.

The specification teaches Zilbergberg determined that single amino acid residues are important for receptor binding and for biological activity of scorpion Na channel toxins (page 1, lines 19-20). The specification provides specific examples which illustrate single amino acid changes cause a substantial decrease in biological activity and others change in structures. The specification also teaches that the role of Na-channels have been less clearly studied (page 1, lines 28-29). The specification briefly describes two toxins which have different chemical and pharmacological properties. The specification concludes that "thus, other toxins derived from scorpion venom will

also have different chemical and pharmacological properties" (page 3, lines 5-10). The specification asserts that SEQ ID NO: 9 is a scorpion neurotoxin I polypeptide (page 3, lines 15-16). The specification compares the neurotoxin I of the instant invention (SEQ ID NO: 9) with the sequence of neurotoxin I from Buthus occitanus tunetanus (SE QID NO: 10) to illustrate the conserved cysteine residues (Figure 2). The specification vaguely alludes to toxin activity assays being confirmed using bioassay, LCMS or antibodies (page 16, lines 5-12). The specification asserts that the presence of toxin activity in the recombinant viruses will be monitored in vivo; compared to wild type; and analyzed using larvae to monitor behavioral changes and mortality (page 16, lines 5-12).

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al. (Toxicon, Vol. 36, No. 8, pages 1141-1154, 1998) also provides various classifications between the different toxins.

The post filing date establishes the existence of at least three pharmacological groups of "long-chain" Na channel toxins characterized from the Chinese scorpion Buthus martensii Karsch (BmK) (Zhu et al. Toxicon, Vol. 38, pages 1653-1661, 2000). There three groups each have different pharmacological characteristics. The first group includes alpha-toxins which affect mammals and/or insects through slowing the sodium channel inactivation, such as BmK1, BmK2, BmK3 etc (page 1654). The third group includes depressants insect selective toxins, which induce progressive flaccid paralysis of insects, such as BmKIT2, BmKIT3 and BmKIT4. The fourth group contains the excitatory insect-selective toxins which cause rapid contractive paralysis of insects upon injection such as BmKIT1 (page 1654). It is clear that each of these "toxins" have different properties, different effects and affect different organisms. Zhu discusses placing 9 novel homologues into various groups based upon various differences in single amino acid residues (page 1659).

Neither the art nor the specification teach the skilled artisan how to use the claimed invention. The art teaches that scorpion toxins are classified into several categories based upon their size, toxicity to certain animals or insects and have different biological and pharmacological characteristics such as whether the toxins are depressant in nature or excitatory. The specification does not teach whether SEQ ID NO: 9 has any particular toxin activity. The specification has assigned SEQ ID NO: 9 as a toxin based upon homology to known toxins. While it is likely that SEQ ID NO: 9 is a

toxin it is unpredictable whether SEQ ID NO: 9 is a toxin to mammals and/or insects and whether the toxin acts in an excitatory or depressant manner. The specification has provided no guidance as to the particular function, specificity or biological activities of SEQ ID NO: 9. Therefore, prior to using the invention, the skilled artisan would be required to perform additional undue experimentation to determine the properties of SEQ ID NO: 9 to be able to use SEQ ID NO: 9 in a meaningful way.

Moreover, the specification fails to provide a clear definition of "having toxin activity." The dictionary provides that toxin is defined as poison produced by living organism (see askoxford.com). Moreover, poison has been defined as substance that when absorbed by living organism kills or injures it. Therefore, it is unclear how one may determine the level of toxin activity required for the claims and how the skilled artisan may determine whether a particular sequence has toxin activity.

With respect to the percent homology language used in the claims, the specification does not teach which particular amino acid residues are important for receptor binding and biological activity. Since the specification has failed to provide any particular characteristics with respect to SEQ ID NO: 9, it would be unpredictable how the skilled artisan could modify the sequence to maintain the particular function of SEQ ID NO: 9. It would require undue and unpredictable experimentation, as described above, to determine the function, biological activity and the pharmacological nature of SEQ ID NO: 9. Furthermore, once the skilled artisan had determined how SEQ ID NO: 9 functions, to modify SEQ ID NO: 9 to maintain the function and properties of the wild-type sequence is unpredictable. The specification has not provided any particular

regions or domains which are essential to the functioning of SEQ ID NO: 9 as a toxin. It is clear from the art, namely Zilberberg, that altering single amino acids within a toxin varies the properties of toxicity vastly (Table 1, page 14812). Therefore, while the skilled artisan could alter four of the amino acids within SEQI DNO: 9 (i.e. 95% identity), it is unpredictable which changes may be made such that toxin activity is maintained.

Therefore weighing all evidence provided in the specification and in the art, the skilled artisan would be unable to practice the claimed invention as a whole without further undue and unpredictable experimentation.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
April 29, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER